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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MOUSE MODEL FOR AUTOIMMUNE DISORDERS

(57) Abstract: A non-human mammalian model of an autoimmune disorder co-expresses a major histocompatibility (MHC) class II-restricted T cell receptor (TCR) and a selected peptide that binds to the TCR. The selected peptide is selectively expressed by MHC class II positive antigen presenting cells (APC) of the mammal. Models with high penetrance of disease are those in which the selected peptide is a MHC class II-restricted T cell determinant that specifically binds with high affinity to the TCR. Models with low penetrance of disease are those in which the selected peptide binds with low affinity to the TCR. These models, which may be transgenic mammals, are used in method for identifying diagnostic and therapeutic markers and targets characteristic of an autoimmune disorder.

WO 2004/042004 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/31519

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : G01N 33/00; A01K 67/027; C12N 15/00, 15/63, 15/85, 15/87, 15/09, 15/70, 15/74, 5/00, 5/02

US CL : 800/3, 18, 21, 22, 25; 435/455, 463, 320.1, 325

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 800/3, 18, 21, 22, 25; 435/455, 463, 320.1, 325

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, MEDLINE, EMBASE, BIOSIS, LIFESCI, WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	RILEY, M.P. et al. Graded Deletion and Virus-Induced Activation of Autoreactive CD4+ T Cells. The J. of Immunology. 2000, Vol 165, pages 4870-4876, see entire	1-5, 11-18, 20-24
Y	BOT et al. Cellular Mechanisms Involved in Protection Against Influenza Virus Infection in Transgenic Mice Expressing a TCR Receptor Specific for Class II Hemagglutinin Peptide in CD4+ and CD8+ T cells. The J. of Immunology. 1998, Vol 160, pages 4500-4507, see entire document.	1-5, 11-18, 20-24
Y	SHIH, F.F. et al. A Major T Cell Determinant from the Influenza Virus Hemagglutinin (HA) can be a Cryptic Self Peptide in HA Transgenic Mice. Int. Immunol. February 1997, Vol 9, No. 2, pages 249-261, see entired document.	1-5, 11-18, 20-24
Y	RILEY, M.P. et al. CD4+ T cells that Evade Deletion by a Self Peptide Dislplay Th1-Biased Differentiation. Eur. J. Immunology. January 2001, Vol. 31, pages 311-319, see entire document.	1-5, 11-18, 20-24

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/31519

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 1-5, 11-18, 20-24

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group I, claim(s) 1-5, 11-18, drawn to methods for generating a non-human mammalian model of an autoimmune disorder by intermating two transgenic mammals of the same species, wherein the first transgenic mammal expresses MHC class I-restricted TCR with high affinity for an A/PR/8 HA peptide S1 and the second transgenic mammal expresses DNA encoding the influenza A/PR/8 HA peptide S1 operably linked to a functional fragment of the MHC class II-I Eα promoter, and the model is a high penetrance model of said disorder .

Group II, claim(s) 1, 6-17, 19, drawn to methods for generating a non-human mammalian model of an autoimmune disorder by intermating two transgenic mammals of the same species, wherein the first transgenic mammal expresses a MHC class II-restricted TCR with high affinity for a synthetic mutant S1 analog of A/PR/8 HA, but with low affinity for the native A/PR/8HA S1 peptide, and the second transgenic mammal expresses DNA encoding the native influenza A/PR/8 HA peptide S1 operably linked to a functional fragment of the MHC class II-I Eα promoter and the model is a low penetrance model of the disorder.

Group III, claim(s) 20-24, drawn to a transgenic non-human mammal that expresses a MHC class II-restricted TCR and expresses a selective peptide that binds to said TCR, wherein the selected peptide is selectively expressed by MHC class II positive APC, wherein said peptide is a naturally occurring, recombinant, or synthetic MHC class II-restricted T cell determinant that specifically binds with high affinity to said TCR, wherein the mammal exhibits high penetrance of said disorder

Group IV, claim(s) 20-23, 25, drawn to transgenic non-human mammal that expresses a MHC class II-restricted TCR and expresses a selective peptide that binds to said TCR, wherein the selected peptide is selectively expressed by MHC class II positive APC, wherein the selected peptide is a naturally occurring, recombinant or synthetic protein or peptide fragment that binds with low affinity to said TCR, wherein the mammal exhibits low penetrance of said disorder.,.

Group V, claim(s) 26-28, drawn to mammalian cells containing at least one transgene comprising a first nucleic acid sequence that encodes a MHC class II-restricted TCR operably linked to regulatory sequences and a second nucleic acid that encodes a selected peptide that binds to said TCR, operably linked to a sequence that directs expression of said selected peptide selectively to MHC class II positive APCs.

Group VI, claim(s) 29-32, drawn to methods of producing a transgenic non-human mammalian model of an autoimmune disorder.

Group VII, claim(s) 33, drawn to a cell culture derived from tissues of a transgenic non-human mammal.

Group VIII, claim(s) 34-35, drawn to methods of screening a compound for the ability to effect symptoms of an autoimmune disorder.

Group IX, claim(s) 36-38, drawn to a method of identifying a gene product responsible for the development of autoimmune disorders

Group X, claim(s) 39-44, drawn to methods for identifying a biochemical marker of autoimmune disorder.

Group XI, claim(s) 45, drawn to a novel composition for the diagnosis or treatment of inflammatory arthritis.

Unity of Invention between different categories of inventions will only be found to exist if specific combinations of inventions are present. Those combinations include:

1) A product and a special process of manufacture of said product
2) A product and a process of use of said product
3) A product, a special process of manufacture of said product, and a process of use of said product
4) A process and an apparatus specially designed to carry out said process
5) A product, a special process of manufacture of said product, and an apparatus specially designed to carry out said process.

The allowed combinations do not include multiple products, multiple methods of using said products, and methods of making multiple products as claimed in the instant invention. See MPEP §1850 and 37 CFR 1.475.

INTERNATIONAL SEARCH REPORT

PCT/US03/31519

The inventions listed as Groups I-XI do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons. Groups I-II, VII, IX-XI are drawn to multiple methods of making and using a non-human mammalian model of an autoimmune disorder, each with specific and materially different protocol that are not required for the implementation of each other. Groups IV-VI, VIII and X are drawn to multiple distinct products that do not share the same inventive concepts that are not required for the implementation of the other.